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Therapeutic Strategies for Acidosis: THAM vs. Sodium Bicarbonate - A comprehensive Review

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Abstract

Metabolic and respiratory acidosis are common challenges in critical care, often necessitating timely intervention to restore physiologic pH and stabilize organ function. Sodium bicarbonate remains the most widely used buffer, but its limitations including Carbon Dioxide (CO_2) generation, risk of hypernatremia, fluid overload, and paradoxical intracellular acidosis have spurred interest in alternative agents. Tris-Hydroxymethyl Aminomethane (THAM) is a biologically inert amino alcohol with a pKa of 7.8 that buffers hydrogen ions without producing CO_2 and partially penetrates the intracellular space. This review critically compares the mechanisms, pharmacokinetics, preclinical and clinical evidence, dosing strategies, and safety profiles of sodium bicarbonate and THAM. Evidence suggests THAM may be particularly advantageous in patients with limited ventilatory reserve, elevated Intracranial Pressure (ICP), hypernatremia, and severe metabolic or mixed acidosis. However, its reliance on renal excretion and side effect profile necessitate careful patient selection. Further clinical trials are warranted to delineate optimal use in contemporary critical care.

Keywords: Increased Intracranial Pressure; Metabolic Acidosis; Sodium Bicarbonate; THAM; Ventilatory Limitation

Introduction

Severe acidosis (pH <7.2) is a frequent and life-threatening condition in critically ill patients, impairing myocardial contractility, increasing arrhythmogenic potential, reducing vascular tone, and diminishing responsiveness to catecholamines [1]. It is estimated that up to 65% of patients admitted to ICU suffer from some form of acidosis [2]. While addressing the underlying cause remains paramount, buffer therapy is often required to temporize physiologic instability. Sodium Bicarbonate ($NaHCO_3$) has historically been the mainstay of therapy, however, its physiologic drawbacks particularly CO_2 generation, intracellular acidosis, and sodium overload have prompted interest in using alternative buffering strategies [3]. Tris-Hydroxymethyl Aminomethane (THAM), developed in the mid-20th century, provides a non-CO_2-generating buffering pathway and offers partial intracellular buffering [4]. Early experimental and clinical studies suggested potential benefits in situations where sodium bicarbonate may exacerbate acidosis, including lactic acidosis, respiratory failure, traumatic brain injury, and fluid-overload states [5]. With recent case reports and systematic reviews revisiting its clinical utility, THAM has reemerged as a candidate for selective use in modern intensive care. This review focuses on THAM versus sodium bicarbonate in the management of acidosis, with particular emphasis on mechanisms, pharmacokinetics, preclinical and clinical data, dosing, monitoring, and clinical decision-making.

Biochemical Mechanisms of Buffering

Sodium Bicarbonate

The buffering action of sodium bicarbonate follows the reaction:

$H^+ + HCO_3^- \rightarrow H_2CO_3 \rightarrow CO_2 + H_2O$

The Bicarbonate ion buffers a proton in the extracellular matrix generating carbon dioxide, which must be cleared by alveolar ventilation. In states of impaired ventilation or permissive hypercapnia (e.g., ARDS), the added CO_2 load may worsen hypercapnia and drive intracellular acidosis [6].

THAM

THAM acts as a proton acceptor without CO_2 generation:

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$THAM + H^+ \rightarrow THAM\text{-}H^+$

Its pKa of 7.8 aligns with physiologic pH, allowing effective buffering of hydrogen ions. Unlike bicarbonate, THAM does not contribute to sodium burden and provides partial intracellular penetration with intracellular buffering. However, its clearance depends on renal function, and accumulation can lead to adverse effects, particularly in Acute Kidney Injury (AKI) [7].

Pharmacokinetics and Elimination

Sodium bicarbonate is highly water-soluble and distributes rapidly in the extracellular fluid compartment. Following intravenous administration, it dissociates into sodium (Na^+) and bicarbonate (HCO_3^-). The bicarbonate component buffers hydrogen ions via the carbonic acid pathway, ultimately generating CO_2 and H_2O [1,2]. This CO_2 rapidly diffuses across cell membranes and requires elimination through alveolar ventilation, making the efficacy of sodium bicarbonate strongly dependent on adequate pulmonary function [8].

Renal handling of sodium bicarbonate is also critical. Under physiologic conditions, filtered bicarbonate is large-ly reabsorbed in the proximal tubule, limiting direct urinary loss. However, in patients with impaired renal func-tion, sodium bicarbonate administration may contribute to sodium and volume overload. Moreover, repetitive dosing can raise serum sodium concentration and osmolality, increasing the risk of hypernatremia, hyperosmolality, and metabolic alkalosis [9]. THAM is a small, biologically inert amino alcohol with a molecular weight of 121 Da and a pKa of 7.8, aligning closely with physiologic pH. It is a weak base that directly binds free hydro-gen ions without generating CO_2, providing an advantage in patients with compromised ventilation. Following intravenous administration, THAM distributes into both extracellular and, to a lesser extent, intracellular com-partments, allowing partial buffering of intracellular acidosis [4,10]. Unlike sodium bicarbonate, THAM is not metabolized but is excreted unchanged via glomerular filtration. Its elimination half-life is therefore highly de-pendent on renal function. In patients with normal renal clearance, THAM is eliminated within 6-12 hours, but in renal insufficiency, accumulation may occur, predisposing to complications such as hyperkalemia, hypogly-cemia, or hepatic dysfunction [10]. Thus, renal function assessment is essential prior to initiation. The pharma-cokinetic differences between sodium bicarbonate and THAM are clinically significant. Sodium bicarbonate is advantageous in patients with intact ventilatory function and preserved cardiac output, where rapid extracellular buffering is required. Conversely, THAM may offer superior performance in patients with limited ventilatory reserve (e.g., ARDS, permissive hypercapnia, severe COPD) or those at risk of sodium overload. However, its efficacy is compromised in the setting of acute kidney injury or oliguria, where clearance is impaired. See Table 1 for Pharmacokinetic Comparison of Sodium Bicarbonate and THAM.

Feature	Sodium Bicarbonate	THAM
Molecular weight	84 Da	121 Da
pKa	6.1 (carbonic acid)	7.8
Distribution	Primarily extracellular	Extracellular + partial intracellular
Mechanism of action	Buffers $H^+ \rightarrow H_2CO_3 \rightarrow CO_2 + H_2O$	Direct H^+ binding $\rightarrow THAM\text{-}H^+$
CO_2 generation	Yes, requires ventilation for clearance	None
Metabolism	Not metabolized	Not metabolized
Elimination	Renal handling of Na^+ and HCO_3^-, indirect via CO_2 exhalation	Renal excretion of unchanged drug
Half-life	Short; dependent on ventilation and renal sodium handling	6-12 hours (normal renal function); prolonged in AKI
Key limitations	CO_2 retention, sodium load, risk of hypernatremia	Requires intact renal function; risk of accumulation in AKI

Table 1: Pharmacokinetic Comparison of Sodium Bicarbonate and THAM.

Evidence from Preclinical Studies

Experimental models of acidosis have long provided a foundation for understanding the differential effects of sodium bicarbonate and THAM. These studies have examined systemic acid-base balance, cardiovascular performance, cerebral physiology, and tissue oxygenation under controlled conditions. Broadly, the preclinical evidence highlights three recurring themes: (1) sodium bicarbonate provides rapid extracellular buffering but at the cost of CO_2 generation and intracellular acidosis; (2) THAM offers effective intracellular

buffering with less ventilatory burden; and (3) the physiological context (ventilatory reserve, renal function, tissue perfusion) determines which agent is preferable [3,4]. Animal models of shock and lactic acidosis have shown that sodium bicarbonate can transiently improve extracellular pH but may impair oxygen unloading and exacerbate intracellular acidosis, potentially worsening myocardial performance [8]. In contrast, THAM has been associated with more stable myocardial contractility and systemic hemodynamics, attributed to its CO_2-independent buffering and intracellular penetration [4]. Some theoretical traumatic brain injury and hypercapnic acidosis models suggest that sodium bicarbonate increases arterial CO_2 tension, leading to cerebral vasodilation and raised intracranial pressure (ICP) [11]. However some studies demonstrate that sodium bicarbonate can lower intracranial pressure and possibly it depends on how the generated carbon dioxide is handled [12]. THAM, by avoiding CO_2 generation, can reduce ICP and improve cerebral perfusion pressure, making it a promising adjunct in neurocritical care [13]. In animal models of acute lung injury, sodium bicarbonate increased arterial CO_2 and worsened ventilatory load, whereas THAM improved systemic pH without raising $PaCO_2$ [3,4]. This finding underscores its potential value in ARDS and permissive hypercapnia strategies, where minimizing ventilatory burden is critical. Preclinical evidence consistently suggests that THAM may outperform sodium bicarbonate in settings of impaired ventilation, high ICP, or profound metabolic acidosis, while sodium bicarbonate remains effective in isolated extracellular acidosis with preserved ventilation. However, THAM's dependence on renal clearance was evident in models of renal failure, where accumulation led to adverse effects [10].

Evidence from Clinical Studies

Clinical trials into sodium bicarbonate and THAM span several decades, encompassing observational studies, randomized trials, and case series across critical care, anesthesia, and neurointensive contexts. While sodium bicarbonate has remained the default buffer, THAM has been selectively studied in patients with respiratory failure, ARDS, traumatic brain injury, metabolic acidosis, and cardiopulmonary bypass [14]. Collectively, the evidence suggests that THAM may provide unique benefits in ventilatory-limited states and in settings where sodium or CO_2 burden is undesirable. In early ICU trials, it has been reported that THAM use in ARDS patients permitted continued permissive hypercapnia while stabilizing arterial pH, without significant CO_2 burden [15]. In contrast, sodium bicarbonate administration in ARDS often worsened CO_2 retention and did not improve survival [16,17]. Hoste et al (2005) conducted a comparative evaluation of buffer therapies in metabolic acidosis and highlighted that THAM produced more sustained correction of intracellular acidosis compared with bicarbonate, although overall survival benefits remained unproven [5]. THAM's unique advantage in controlling Intracranial Pressure (ICP) makes it preferable in the context of neurocritical care. A case series documented that THAM reduced ICP in traumatic brain injury and stroke patients without increasing $PaCO_2$, unlike sodium bicarbonate, which could theoretically raise ICP due to cerebral vasodilation if $PaCO_2$ increases and goes unchecked [13]. In mechanically ventilated patients with severe hypercapnia, sodium bicarbonate often worsens ventilatory load by increasing CO_2 generation. Clinical studies demonstrated that THAM can safely buffer acidosis without exacerbating hypercapnia, allowing clinicians to maintain lung-protective ventilation strategies in ARDS [7]. THAM has been studied as an adjunct during Cardiopulmonary Bypass (CPB) and ECMO, where acid-base disturbances are common. Some studies reported improved metabolic control and reduced lactate accumulation with THAM, though large-scale evidence remains limited [14]. Despite encouraging findings, THAM studies are limited by small sample sizes, heterogeneity, and absence of large randomized controlled trials. Sodium bicarbonate, by contrast, has an extensive evidence base, though most data show modest physiologic improvements without clear survival benefit. Modern practice thus reserves THAM for highly selective patients where bicarbonate is contraindicated or ineffective [18]. See Table 2 for the summary of key clinical evidence between sodium bicarbonate and THAM.

Clinical Setting	Sodium Bicarbonate	THAM
General ICU acidosis	Rapid extracellular buffering; worsens CO_2 retention; risk of hypernatremia	Sustained pH correction; avoids CO_2 generation; efficacy dependent on renal clearance
ARDS / Permissive Hypercapnia	Increases $PaCO_2$, may worsen acidosis	Improves pH without increasing $PaCO_2$; supports protective ventilation
Traumatic Brain Injury / Stroke	Raises ICP via CO_2-mediated vasodilation	Lowers ICP, improves cerebral perfusion
Cardiac Surgery / ECMO	Used routinely; risk of sodium load	Improves metabolic control, less sodium burden
Refractory Lactic Acidosis	Limited benefit; CO_2 retention problematic	Case reports of efficacy, but data sparse

Table 2: Summary of Key Clinical Evidence.

Clinical Indications and Contraindications

Sodium bicarbonate remains the primary buffer in the management of acute metabolic acidosis and is widely recognized as first-line therapy when rapid extracellular pH correction is required [16,19]. Its clinical utility is most evident in patients with severe metabolic acidosis, particularly when arterial pH falls below 7.1 and hemodynamic instability is present perhaps in the presence of acute kidney injury [9,17,19]. In addition, sodium bicarbonate plays an important role in the management of hyperkalemia, where it serves as a temporizing measure to shift potassium into cells while definitive therapy is arranged [9]. Toxicologic emergencies also represent a classic indication: tricyclic antidepressant overdose, salicylate poisoning, and sodium-channel blocker toxicity are well-established scenarios in which bicarbonate administration improves survival and mitigates cardiotoxicity [9]. Furthermore, sodium bicarbonate is indispensable in bicarbonate-wasting states, such as renal tubular acidosis or diarrheal syndromes characterized by significant bicarbonate loss [20]. Despite its widespread use, sodium bicarbonate must be employed judiciously, as its administration in patients with impaired ventilation may exacerbate CO_2 retention, thereby worsening intracellular acidosis even as extracellular parameters improve [9]. THAM, by contrast, is not a universal substitute for bicarbonate but occupies well-defined clinical niches where it offers distinct advantages. Its primary role lies in respiratory-limited states, such as Acute Respiratory Distress Syndrome (ARDS), Chronic Obstructive Pulmonary Disease (COPD), or situations where permissive hypercapnia is employed as part of a lung-protective ventilation strategy [18]. In such contexts, bicarbonate is often contraindicated because of the risk of worsening hypercapnia, whereas THAM can correct systemic pH without generating additional CO_2. A second indication is in neurocritical care, where THAM has demonstrated efficacy in lowering intracranial pressure in patients with traumatic brain injury, ischemic stroke, or post-cardiac arrest encephalopathy complicated by acidosis [13].

THAM also provides a useful alternative in patients for whom sodium load would be harmful, such as those with hypernatremia, congestive heart failure requiring fluid restriction. Finally, in refractory metabolic acidosis that is unresponsive to bicarbonate therapy-such as severe lactic acidosis or sepsis, THAM has been employed as a rescue therapy with encouraging results in limited studies [7,21]. Despite these promising applications, both buffers carry important contraindications that restrict their use. Sodium bicarbonate should be avoided, or at least used with extreme caution, in the presence of severe hypernatremia, in patients with significant volume overload due to heart failure or renal insufficiency, and in those with impaired ventilation, where additional CO_2 burden could precipitate further physiologic compromise [9,21]. THAM should be used with caution in patients with renal failure or oliguria, since the drug is eliminated unchanged by glomerular filtration and accumulation can lead to toxicity [10]. Hepatic dysfunction also represents a relative contraindication, as reversible hepatotoxicity has been reported with prolonged or high-dose use [10]. In addition, THAM may exacerbate hypoglycemia, making it unsuitable for patients prone to low glucose levels, such as malnourished or critically ill individuals receiving intensive insulin therapy [7]. Finally, pediatric patients with immature renal function are considered a relative contraindication group, reflecting the risk of impaired drug clearance and adverse effects in this vulnerable population [10]. In summary, while sodium bicarbonate remains the default buffer for rapid correction of severe extracellular acidosis, THAM occupies an important but more selective role, particularly in contexts where ventilation, sodium balance, or intracranial dynamics preclude the use of bicarbonate. Careful patient selection and awareness of contraindications are therefore essential in determining which

buffer, if any, should be administered. See Table 3 for clinical indications and contraindications of Sodium Bicarbonate vs THAM.

Category	Sodium Bicarbonate	THAM
Primary indications	Severe metabolic acidosis (pH <7.1); hyperkalemia; toxin-induced acidosis; bicarbonate-wasting states	Respiratory-limited states (ARDS, COPD, permissive hypercapnia); elevated ICP; hypernatremia or sodium overload; refractory metabolic acidosis
Advantages	Widely available; familiar dosing; rapid extracellular effect	No CO_2 generation; partial intracellular buffering; reduces ICP; avoids sodium burden
Limitations	Generates CO_2 (↑ventilatory load); sodium overload; paradoxical intracellular acidosis	Requires intact renal clearance; potential hepatotoxicity, hypoglycemia; limited availability
Contraindications	Hypernatremia, volume overload, severe ventilation impairment, metabolic alkalosis	Renal failure/oliguria, hepatic dysfunction, neonates/ immature renal function

Table 3: Clinical Indications and Contraindications of Sodium Bicarbonate vs THAM.

Dosing Strategies

The dosing of buffer therapy in critical care requires a careful balance between achieving adequate correction of acidemia and avoiding iatrogenic complications. Sodium bicarbonate dosing has traditionally been guided by the calculated base deficit, with the general formula involving body weight and bicarbonate deficit to estimate requirements. In practice, clinicians often administer incremental doses, reassessing Arterial Blood Gases (ABGs) and hemodynamic parameters to avoid overshoot alkalosis. The onset of action is rapid, but its effect is short-lived due to redistribution and renal elimination, necessitating repeated boluses or continuous infusions in ongoing acidosis [6,9]. This approach is particularly relevant in conditions such as renal tubular acidosis, toxic ingestions, or hyperkalemia, where sodium bicarbonate's well-characterized physiologic effects provide both diagnostic and therapeutic benefit [20].THAM, in contrast, follows a slightly different dosing paradigm because of its unique pharmacokinetic and physiologic profile. The standard approach involves calculating the dose based on lean body weight and the magnitude of base deficit, using the formula [7,10]: Volume of 0.3 mol/L THAM (mL) = 1.1 × lean body weight (kg) × base deficit (mmol/L). The factor "1.1" is considered as an adjustment for the presence of acetic acid with anticipated lowering of buffering capacity by 10% [10]. Unlike sodium bicarbonate, which is often given in boluses, THAM therapy generally begins with a loading dose amounting to approximately 25% of the calculated total requirement, followed by infusion of the remainder over one to two hours. This gradual administration mitigates the risks of hypoglycemia and respiratory depression, which are more likely with rapid infusion. In patients with respiratory acidosis or elevated intracranial pressure, continuous infusions at rates of 1 to 2 mL/kg per hour equivalent to approximately 0.55 mmol/kg per hour are typically employed, providing stable buffering while avoiding sharp fluctuations in acid-base status [7].

Certain safety thresholds must be considered with THAM. The maximum recommended rate of administration is 2 mmol/kg over 30 minutes (or 500mg/kg over one hour), beyond which the risks of respiratory depression and osmotic shifts increase substantially. In patients with impaired renal function, dosage reductions are mandatory given THAM's reliance on glomerular filtration for elimination [18]. For these individuals, infusion rates should not exceed 40 mmol per hour, and treatment duration should be limited to two or three days unless close monitoring for osmotic complications is feasible [7,8,10]. Daily maximum dosing also varies according to the patient's ventilatory status and renal function. In spontaneously breathing patients, a ceiling of 7 mmol/kg per 24 hours is advised to minimize adverse effects [7,10]. Mechanically ventilated patients, by contrast, may tolerate higher doses of up to 15 mmol/kg per 24 hours, particularly when THAM is used for extended periods, sometimes up to ten days-in the setting of refractory acidosis. For patients with acute kidney injury or chronic kidney disease, however, the daily maximum should not exceed 7 mmol/kg per 24 hours, reflecting the impaired clearance and increased risk of accumulation and not exceeding 2-3 days [10]. Taken together, these dosing strategies emphasize the importance of tailoring buffer therapy not only to the severity of acidosis but also to the underlying pathophysiologic context and the patient's capacity to clear the administered agent. Sodium bicarbonate remains favored in situations requiring rapid extracellular correction, whereas THAM is reserved for specific scenarios in which avoidance of CO_2 generation, sodium load, or hyperosmolar complications is particularly advantageous. See Table 4 for dosing strategies between sodium bi-carbonate and THAM.

Parameter	Sodium Bicarbonate (in mmol)	THAM (ml of 0.3M)
Formula	0.3 × BW (kg) × base deficit. Administered as 8.4% (1 mmol/mL) or 7.5% solution.	1.1 × BW (kg) × base deficit. Use THAM acetate, not THAM base (base formulation causes tissue necrosis)
Route	IV bolus/infusion	IV infusion (loading =25% of the calculated dose + maintenance = rest 75% over the next 1-2 hours)
Special uses	Cardiac arrest: 1 mmol/kg; hyperkalemia: 50 mmol IV	Continuous infusion for respiratory acidosis/ICP (1-2 mL/kg/h (≈0.55 mmol/kg/h))
Max daily dose	No strict cap, guided by pH/ABG	7 mmol/kg (spontaneous); 15 mmol/kg (ventilated)
Key risks	Hypernatremia, volume overload, CO_2 retention	Renal clearance required; hypoglycemia; osmotic effects

Table 4 : Dosing Strategies of Sodium Bicarbonate vs THAM.

Monitoring and Adverse Effects

The clinical use of buffer therapy requires vigilant monitoring to optimize efficacy and prevent complications. With sodium bicarbonate, Arterial Blood Gas (ABG) analysis remains the cornerstone of follow-up. Frequent sampling is necessary to assess systemic pH, $PaCO_2$, and base excess, as the generation of CO_2 following bicarbonate administration can transiently worsen acidosis if ventilatory clearance is inadequate. In parallel, serum electrolytes should be monitored, since sodium bicarbonate therapy may provoke hypernatremia and hypokalemia [9]. Serial measurement of serum osmolality is particularly important during high-dose therapy, where hyperosmolar states and volume overload may develop. Careful clinical evaluation of fluid balance is warranted, especially in patients with congestive heart failure or renal impairment, as these populations are particularly susceptible to pulmonary edema [9]. Neurologically, bicarbonate can paradoxically worsen cerebral acidosis, given that CO_2 diffuses rapidly across the blood-brain barrier and lowers cerebrospinal fluid pH despite an apparent improvement in systemic parameters [9,11,17]. THAM requires a somewhat different monitoring strategy. Because it is cleared unchanged by the kidneys, close assessment of renal function including urine output, serum creatinine, and estimated glomerular filtration rate is mandatory [10,11,18]. In patients with impaired renal clearance, accumulation of THAM can lead to serious toxicity. ABG analysis remains important to guide therapy, though THAM often provides a more sustained correction of systemic pH compared with bicarbonate. Electrolyte monitoring should include potassium, as systemic alkalinization may contribute to hyperkalemia, and glucose, since hypoglycemia has been reported as a distinct adverse effect [7,18]. In patients receiving prolonged courses or higher cumulative doses, liver function tests should be assessed, given documented cases of reversible hepatotoxicity [10].

Adverse effects also differ meaningfully between the two agents. Sodium bicarbonate is associated with hypernatremia, hyperosmolality, and volume overload due to its sodium load [9]. Its CO_2-generating nature predisposes to paradoxical intracellular acidosis and can impair tissue oxygen delivery by shifting the oxyhemoglobin dissociation curve. Hypokalemia is a frequent accompaniment, resulting from intracellular potassium shifts during systemic alkalinization [9]. By contrast, THAM avoids sodium and CO_2 load but introduces risks tied to renal clearance and metabolic disturbances. Hyperkalemia may occur during alkalinization, while hypoglycemia represents another metabolic liability [7]. Hepatotoxicity has been reported but appears reversible upon discontinuation. Local complications such as infusion site irritation and, in cases of extravasation, soft tissue necrosis have also been described (especially with the THAM base, less with THAM acetate) [10]. Rarely, severe electrolyte shifts may provoke seizures [10]. Despite these encouraging findings, the evidence base for THAM is limited by several important gaps. Most studies are small, single-center investigations, often conducted decades ago, with heterogeneous populations and variable dosing strategies. Long-term outcomes such as survival, neurologic recovery, or organ support requirements have rarely been assessed. Large-scale randomized controlled trials directly comparing THAM and bicarbonate are absent, leaving clinicians to extrapolate from physiologic data and limited case experience. Moreover, access to THAM is inconsistent across healthcare systems, further restricting opportunities for systematic study. By contrast, sodium bicarbonate has been evaluated in larger cohorts and in more diverse patient populations, but its benefits remain largely physiologic rather than outcome-driven. The BICAR-ICU trial, for example, showed that bicarbonate improved survival only in the subgroup of patients with severe acidosis and concomitant acute kidney injury, underscoring its limited but still relevant therapeutic niche [17]. No equivalent modern trial has tested THAM in a similarly rigorous fashion, leaving a critical evidence gap regarding whether its unique physiologic benefits translate into meaningful clinical advantages. Future research must therefore focus on adequately powered randomized trials, particularly in

populations such as ARDS, traumatic brain injury, and ECMO, where THAM's theoretical benefits may prove clinically significant. Until such evidence is generated, the choice between these two agents remains guided less by definitive outcome data than by clinical judgment, pathophysiologic rationale, and the patient's specific risk profile.

Future Directions and Research Priorities

Several future research avenues are therefore apparent. The first involves large-scale Randomized Controlled Trials (RCTs) directly comparing sodium bicarbonate and THAM in specific patient populations. For example, in Acute Respiratory Distress Syndrome (ARDS) where permissive hypercapnia is employed, THAM could be rigorously tested against sodium bicarbonate to determine whether its physiologic advantages translate into reduced ventilatory burden, improved oxygenation, and better survival. A similar need exists in neurocritical care, particularly in traumatic brain injury and ischemic stroke patients with concurrent acidosis, where THAM may reduce intracranial pressure without worsening cerebral hemodynamics-a hypothesis that requires systematic evaluation. A second priority is the integration of buffer therapy into organ support strategies such as Extracorporeal Membrane Oxygenation (ECMO) and Renal Replacement Therapy (RRT). Preliminary reports suggest that THAM may reduce lactate accumulation and stabilize acid-base balance during ECMO and cardiopulmonary bypass, but these findings have never been confirmed in robust trials. Coordinated studies incorporating modern critical care practices could clarify whether buffer therapy influences not just laboratory values but also clinical outcomes such as time on mechanical ventilation, vasopressor dependence, and ICU length of stay. Third, further research is warranted into the long-term metabolic and neurologic effects of THAM. Reports of reversible hepatotoxicity and hypoglycemia highlight the need for careful pharmacovigilance, particularly with prolonged or high-dose infusions. Longitudinal studies could determine whether such adverse effects carry any clinical sequelae or are of limited practical significance. Parallel investigations into pharmacokinetics in populations with renal impairment, liver dysfunction, and varying degrees of critical illness would also refine dosing strategies and improve safety. Finally, there is a need for comparative cost-effectiveness and availability analyses. Sodium bicarbonate is inexpensive, globally available, and well integrated into protocols, while THAM's use is sporadic, often limited to tertiary or academic centers. Without broader access, the feasibility of conducting multi-center RCTs and implementing practice changes will remain limited. A coordinated effort involving critical care networks, academic investigators, and pharmaceutical stakeholders may be necessary to ensure THAM's availability for rigorous study. Until such data emerge, clinical practice will remain shaped by the interplay of tradition, physiologic reasoning, and individual patient factors rather than definitive evidence

Conclusion

The management of metabolic acidosis in critical illness remains a cornerstone of intensive care, yet the choice of buffer therapy continues to provoke debate. Sodium bicarbonate, the traditional agent, offers predictable extracellular alkalinization and remains indispensable in scenarios such as toxin-induced acidosis, bicarbonate-wasting states, and profound acidemia with hemodynamic instability especially when associated with acute kidney injury. Its physiologic limitations, however including CO_2 generation, paradoxical intracellular acidosis, sodium overload, and the potential to exacerbate intracranial hypertension-restrict its utility in patients with impaired ventilation, fluid overload, or neurologic vulnerability. THAM represents an alternative approach, ca-pable of buffering protons without generating CO_2 and of partially correcting intracellular acidosis. Clinical evi-dence, though limited, supports its use in ventilatory-limited states such as ARDS with permissive hypercapnia, as well as in neurocritical care where control of intracranial pressure is paramount. Its advantages in sodium-restricted patients and in cases of refractory acidosis unresponsive to bicarbonate further underscore its niche potential. Yet THAM is not without drawbacks: its dependence on renal clearance, potential for hepatotoxicity and hypoglycemia, and limited global availability all pose challenges to broader adoption. The comparative literature highlights an asymmetry: sodium bicarbonate is supported by a broad but largely physiologic evi-dence base, while THAM is supported by narrower but more mechanistically compelling data. Neither agent has yet demonstrated consistent survival benefit across large-scale trials, leaving the clinician to rely on patient-specific factors, underlying pathophysiology, and the balance of risks and benefits. Future progress will depend on high-quality randomized controlled trials, particularly in populations such as ARDS, traumatic brain injury, and ECMO, where THAM's theoretical advantages may prove clinically meaningful. Until then, buffer therapy remains a domain where careful judgment must substitute for definitive evidence. The decision to employ sodi-um bicarbonate or THAM should be individualized, guided by the unique physiologic needs and vulnerabilities of each patient, and always accompanied by rigorous monitoring to mitigate iatrogenic harm.

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